

**13th Congress of the Asia Pacific Blood and Marrow Transplantation
(APBMT) Group, Taipei, Taiwan, April 25-27, 2008**

Report on Treatment Trends for Fungal Infections

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Introduction

Asia Pacific Blood and Marrow Transplantation (APBMT) Group meetings aim at promoting all aspects of basic and clinical research associated with haematopoietic stem cell transplantation (HSCT). Delegates attending the 13th Congress of the APBMT Group held in Taipei, Taiwan from April 25-27, 2008, learnt of the latest advances in this field, including education, standardisation, quality control, and accreditation for transplant procedures.

This report focuses on invasive fungal infections (IFIs), which are a severe clinical complication in immunocompromised patients, particularly for those with haematological malignancies undergoing HSCT.

The increasing incidence of IFIs and the changing epidemiology of the pathogens responsible for them have led to a surge of interest in when and how to treat these infections. While it is recognised that antifungals must be initiated early if treatment is to be successful, it is very difficult to get a definitive diagnosis of an IFI. This has led to a number of different strategies being employed, ranging from prophylactic therapy aimed at preventing fungal infection from occurring, to later treatment, when therapy is initiated after early signs of infection have appeared.

Interest in the optimal timing of antifungal therapy has increased since the development of the Australasian Consensus Guidelines - *Recommendations for Prophylaxis in Haematology/Stem Cell Transplant (SCT) in Patients with Graft Versus Host Disease*. [1] These recommend the use of posaconazole as prophylaxis in patients who are at high risk of a fungal infection and who have received an allogeneic stem cell transplant (SCT).

Issues discussed at the Taipei meeting included when to initiate antifungal therapy, recent advances in treatments, non-culture based methods of diagnosing IFIs and the Australasian guidelines.

Changing epidemiology of invasive fungal infections

Invasive fungal infections present an important challenge to haematology, oncology and intensive care practices. Epidemiological studies show an increasing number of infections occurring in immunosuppressed patients. Speaking at the Schering-Plough satellite symposium, *Advances in the Management of Fungal Infections*, **Dr Monica Slavin**, Royal Melbourne Hospital, Australia, identified patients most at risk of IFI. Risk factors include:

- Increasing age
- Acute Myeloid Leukaemia (AML)
- Neutropenia – the risk increases with increasing duration and depth of neutropenia
- High-dose corticosteroids
- Graft vs. Host Disease (GVHD)

‘Patients with advanced disease who are responding poorly and have a low T-cell count are most at risk.’ said Dr Slavin.

While *Candida* remains the most common yeast infection and *Aspergillus* the most common mould infection, there is now a significant change in the species encountered. A recent survey in Melbourne of patients with acute leukaemia reported by Dr Slavin showed that while *Aspergillus* still accounted for 33% of mould infections, *Scedosporium*, *Zygomycetes* and *Fusarium* species were beginning to be seen more frequently. [2] According to Dr Slavin, there are a number of reasons for this shift in epidemiology. These include:

- Selection pressure on the fungal species
- More aggressive immunosuppression
- T-cell depletion

- Increasing age
- More HSCT recipients
- Monoclonal antibodies used separately or in combination
- Better identification of fungal infections
- Environmental changes in buildings

Dr Slavin added that the increase in *Fusarium* and *Zygomycetes* species is a matter for concern, because they tend to be very drug resistant and mortality rates are very high. However, posaconazole, an extended-spectrum triazole that was approved for use in Australia in March 2006, has an extended spectrum of activity against many invasive fungi. In three studies reported by Dr Slavin, posaconazole was found to be effective when used as salvage treatment for refractory invasive aspergillosis (relative response rate of 42%) [3], refractory zygomycosis (relative response rate of around 60%) [4] and refractory fusariosis (relative response rate 46%) [5].

2008 Australasian Consensus Guidelines: Recommendations for Prophylaxis in Haematology/Stem Cell Transplants

Dr Slavin presented the 2008 Australasian Consensus Guidelines' recommendations for prophylaxis in haematology/stem cell transplants. [1] She advised that the group which developed the guidelines had used the National Health and Medical Research Council (NHMRC) grading system for its recommendations, which are:

A – Body of evidence can be trusted to guide practice

B - Body of evidence can be trusted to guide practice in most situations

C - Body of evidence provides some support for recommendations but care should be taken in this application

D - Body of evidence is weak and recommendations must be applied with caution

Acute Myeloid Leukaemia (AML)

Setting	Recommended prophylaxis	Alternative
Intensive treatment AML: Induction, re-induction	Posaconazole 200mg oral TDS (B)	Itraconazole 200mg oral solution BD (B)
AML consolidation with high-dose therapy	Posaconazole 200mg oral solution TDS (B)	Itraconazole 200mg oral solution BD (B)
AML less intensive therapy	Fluconazole 200mg/day oral (D) or no prophylaxis (B)	

Allogeneic Stem Cell Transplant

Setting	Drugs	Alternative
Standard Allogeneic-SCT pre-engraftment	Fluconazole oral 400mg/day at admission to day 75 (B)	
Higher-risk Allogeneic-SCT pre-engraftment, cord blood, unrelated BM	Posaconazole 200mg oral TDS (no grading) If no GVHD, fluconazole through day 75 once neutropenia has resolved	Itraconazole 200mg BD (B)
Allogeneic-SCT with grade 2-4 GVHD	Posaconazole 200mg TDS until day 112 post-onset GVHD or resolution (B)	Itraconazole 200mg BD (B)
Autologous-SCT with mucositis chemotherapy regimen	Fluconazole 200-400mg day oral (C) or no prophylaxis if no mucositis expected	

To show the effects of prophylactic treatment, Dr Slavin presented results of a comparative retrospective study in Australia. [2] This looked at prophylaxis antifungal treatment in 175 patients with AML during the period 1997-2007. Results showed that itraconazole (median dose 150mg BD), voriconazole (200mg BD) and posaconazole (200mg TID) were all effective at reducing the numbers of proven/probable IFIs (6%, 1% and 2% respectively) in the study period. However, fluconazole (200mg/day) was not as effective with 11% proven/probable IFIs. Deaths due to IFIs were also reduced by antifungal prophylaxis with no deaths in the voriconazole and posaconazole arms; 2 deaths with itraconazole; and 4 deaths with fluconazole.

'Traditional diagnoses of IFIs are made late but new diagnostic tools such as PCR and Beta-D glucan tests are being developed, which will aid earlier diagnosis,' said Dr Slavin. 'However, I am still learning to use these tests, so I will stick with prophylaxis for the time being.'

IFIs in Allogeneic Transplantation

Speaking at the Schering-Plough satellite symposium **Dr Daniel Couriel**, Sarah Cannon Blood and Marrow Transplantation Program, Nashville, Tennessee, outlined some of the risk factors that affect patients undergoing allogeneic HSCT. 'During the pre-engraftment phase (<30 days), bacterial infections and neutropenia are common and patients are very susceptible to all *Candida* and *Aspergillus* species,' he said. 'In the post-engraftment phase (30-100 days), patients are still susceptible to infections such as pneumocystis and CMV. During the late phase (>100 days), Graft Vs Host Disease (GVHD), which affects around 50% of allogeneic transplants, can be a huge problem.'

Dr Couriel said that the median time for immunosuppression in this group of patients was 23 months but that 15% of patients with GVHD are still immunosuppressed after seven years.[6] 'Infections cause a lot of mortality in this group with 62.7% dying of an infection, especially from an IFI.'

Data from a large trial, reported by Dr Couriel, show that the use of the broad-spectrum triazole posaconazole as antifungal prophylaxis can reduce the incidence of IFIs as well as reduce the overall mortality in these high-risk patients.

The trial compared posaconazole and fluconazole for prophylaxis of IFI in allogeneic HSCT recipients with GVHD who were receiving intensive immunosuppressive therapy.[7] Patients were randomised to oral posaconazole (200 mg three times a day, 301 patients) or oral fluconazole (400 mg once daily, 299 patients). Treatment was given for 16 weeks or until a pre-specified endpoint had been reached. At the end of the 16-week period, posaconazole was found to be superior to fluconazole in preventing proven or probable invasive aspergillosis (7 cases vs. 27 cases, $p=0.006$). It was found to be as effective as fluconazole in preventing all IFIs (16 cases vs. 27 cases, $p=0.07$). Posaconazole was also superior in preventing aspergillosis (5 cases vs. 17 cases, $p=0.004$) and IFIs overall (7 cases vs. 22 cases, $p=0.004$). Mortality due to invasive IFIs was lower for posaconazole (1%) than fluconazole (4%) ($p=0.041$) and both drugs were well tolerated.

Dr Couriel emphasised that to avoid problems such as over-treatment, high costs and possible toxicity, antifungal prophylaxis needs to target the highest-risk patient population. 'Within the 'targeted' setting posaconazole looks very promising and has received an A1 recommendation as prophylaxis in allogeneic-HSCT recipients in the latest guidelines from the Infectious Diseases Society of America (IDSA).' [8]

When to give antifungal therapy

Deciding when to initiate therapy is difficult, as diagnosing mould infections can be problematic, according to **Dr Johan Maertens**, University Hospitals, Leuven, Belgium. Speaking at the Pfizer satellite symposium, *Updated treatment trends for IFIs in patients with haematological malignancies*, Dr Maertens said that many patients are too sick for bronchoscopy and many will also have negative blood cultures and non-specific changes in their chest x-

rays. He added, however, that a halo sign is predictive of a fungal infection and patients offered antifungals based on the presence of a 'halo' do better compared to those who are treated later.

Dr Maertens suggested that in order to justify empirical or prophylactic treatment three questions should be asked:

- Can the infection be treated easily?
- Are adverse drug reactions likely?
- Is the infection easily diagnosed?

If the answer to all these questions is 'no' then prophylaxis is justified. If the answers are 'yes' to all the questions, then prophylaxis/empirical treatment is not justified. Dr Maertens thinks that, in the absence of sophisticated diagnostic tools and in the presence of prolonged neutropenia despite antibiotic therapy or recurrent fever following initial resolution, empirical antifungal therapy is probably the best approach. He also stated that it was important to reduce the risk of an IFI by preserving organ function and patients' immune status, as well as optimising first line antifungal therapy.

Recommendations based on the recent European Conference on Infections in Leukaemia (ECIL) guidelines give an A1 grading to posaconazole prophylaxis in patients undergoing chemotherapy and autologous transplantation and an A1 grading to fluconazole and posaconazole prophylaxis in patients with GVHD who are undergoing immunosuppressive therapy. [9]

REFERENCES

1. Slavin MA, Heath CH, Thursky KA, et al. Antifungal prophylaxis in adult stem cell transplantation and haematological malignancy. *Internal Medicine Journal* 2008;38:468-476
2. Downey MT, Slavin MA, Thursky KA, et al. Invasive mould infections in patients undergoing treatment for acute leukemia at the Royal Melbourne Hospital, presented at Haematology Society of Australia and New Zealand Annual meeting, Melbourne, October 2004, abstract number 157
3. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007;44:2-12

4. Van Burik JH, Hare RS, Solomon HF, et al. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 81 cases. *Clin Infect Dis* 2006;42:e61-65
5. Raad I, Hachem RY, Herbrecht R, et al. Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. *Clin Infect Dis* 2006;42:1398-1403
6. Stewart BL, Storer B, Storek H, et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. *Blood* 2004;104(12):3501-3506
7. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356(4):335-47
8. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46:327-60
9. Guidelines from the First European Conference on Infections in Leukaemia: ECIL 1. *European Journal of Cancer* 2007; 5 (suppl): 1-59